

## Review Article

# The overlap between gastroesophageal reflux disease and irritable bowel syndrome: an updated systematic review

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## ABSTRACT

Evidence shows that a degree of overlap is detected between gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS). In this review, we aim to update the current evidence from recent studies published in the last decade. Electronic and manual search strategies were both conducted to look for studies that reported the association between gastroesophageal reflux disease and IBS from 2011 to January 2021. We have included all study designs to formulate updated evidence and report all the potential outcome measures. We included a total of 16 studies on a total of 146,156 patients, collectively. Out of these studies, 14 were cross-sectional while only two were randomized controlled trials. The frequency of overlap was hugely variable among the results of the included studies, ranging between 1.7 and 74.7%. Almost all studies used the Rome III criteria for IBS and used questionnaire-based assessment for gastroesophageal reflux disease patients. Female gender and cigarette smoking were the commonest most significant risk factors for developing the overlap. Intestinal hypersensitivity, hyperactive gastric acids, and generalized abnormal motility of the digestive tract were the commonest theories. Obtained evidence remains strong, indicating the overlap between IBS and gastroesophageal reflux disease patients, however, the definite explanation remains non-clear and further studies are needed.

**Keywords:** GERD, Irritable bowel syndrome, Overlap, Epidemiology

## INTRODUCTION

The definition of functional gastrointestinal disorders (FGIDs) includes a variety of chronic symptoms and signs that affect the gastrointestinal tract which usually occur in combinations and does not necessarily alter any biochemical and structural components in the physiology of the intestine, according to the Rome IV criteria.<sup>1</sup>

Evidence shows that the overall prevalence of these disorders affects around one-third of the global general population.<sup>2</sup> As previously stated, FGIDs include a variety of gastrointestinal clinical pictures. These can affect multiple areas of the tract. Moreover, evidence shows that multiple comorbidities can simultaneously occur at different intestinal regions within the same patient.<sup>3</sup> Disorders causing functional dyspepsia (FD),

like GERD, and irritable bowel syndrome are the commonest FGIDs.

GERD is a common disorder of the upper gastrointestinal tract with a high prevalence rate in the general population.<sup>4</sup> Previous reports showed that around 40% of the United States population frequently complain about relevant esophageal symptoms, and around 10-20% of them complain from these symptoms on a weekly basis.<sup>5</sup> It also impact the quality of life of those affected patients and the elevated cost-related to care and management. The pathophysiology behind GERD development is mainly attributable to the mucosal damage secondary to the abnormal passage of gastric contents through an incompetent gastroesophageal junction. This leads to the development of many symptoms such as retrosternal heartburn and food regurgitation. The clinical diagnosis of this condition is built on the history of these symptoms, in addition to the characteristic relief after administration of proton pump inhibitors (PPIs).<sup>6,7</sup>

Many studies have been published that have investigate the association between the different varieties of FGIDs, with many of them focusing on the correlation between IBS and GERD, specifically.<sup>8-10</sup> Jung et al even reported that the rate of co-occurrence of these conditions is probably more common than the expected rates.<sup>9</sup> This phenomenon can be explained by the presence of a general sensory and motor function in the gastrointestinal tract. Consequently, evidence suggests that these disorders probably have common risk factors and pathophysiological mechanisms that need further investigations. Despite many reviews reporting this, none of it have recently investigated the growing evidence regarding the association of GERD and IBS within the last decade.<sup>9,11</sup> Therefore, the present study aims at collecting and updating new evidence from the current studies in the literature that reported the correlation between GERD and IBS.

### **Search strategy**

We have conducted a thorough search strategy to include all of the relevant articles based on our inclusion criteria. The search term included all of the following key-words and their synonyms to find all the relevant articles: ("Irritable bowel syndrome" or "functional diarrhea" or "functional constipation" or "spastic colon" or IBS) and ("gastroesophageal reflux" or GERD or "gastro-esophageal reflux" or "gastro-oesophageal reflux" or GORD or reflux or "24-hour pH"). We used this term in the relevant databases including PubMed, web of science, scopus, google scholar, the international standard randomised controlled trial number, the Cochrane library, and the world health organization virtual health library. We included studies that published their results in English and article that were published from 2011 up to the date this study was conducted (January 2021). Searching the references of the included studies and the relevant reviews were also conducted to include any study that we

might have missed using our systematic search strategy. The manual search was also done according to our inclusion and exclusion criteria.

### **Inclusion and exclusion criteria**

We targeted all study designs that investigated the association between GERD and IBS that was published from 2011 up to January 2021 and assessed their outcomes on human subjects. Moreover, for a study to be included, a clear definition of GERD and IBS should be included within the literature of the study. We aimed to assess the prevalence and associated factors between the two disorders from the included studies. Therefore, we excluded studies that overlapped the above information and did not investigate the association between the two disorders or did not clearly state the prevalence rate of either of the two modalities within a population of patients that had the other modality at baseline. We also excluded articles that were published in non-English languages, abstract-only articles, incomplete and non-original studies as reviews, thesis, protocols, and editorials.

### **Screening and data extraction**

This step was conducted following the previously published and widely-known preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.<sup>12</sup> After we finished searching the relevant databases, we imported these results into a unified endnote library to identify and exclude all the possible duplicated citations. The grouped results were then exported to an excel sheet that was prepared for the next step: title and abstract screening. The excel sheet included information about the reference of the included study as ID, authors, title, publication year, DOI, URL, journal, and abstracts. If an abstract was missing, members had to search the relevant journals to retrieve the study abstract. The screening was done by two authors who were blinded to each others' results to achieve the best outcomes from the process. After finishing their screening, four authors compared their results in a public group discussion under the senior author's supervision. Full-texts of the included articles were then retrieved to presume the screening process to include the potential studies.

For data extraction to take place, a standardized excel sheet was needed. Consequently, two of the authors collaborated to design a suitable sheet that suits our criteria and intended outcomes. At first, a pilot sheet was performed based on the outcomes of some of the included studies. After that, the sheet was rigorously modified multiple times based on the designs and outcomes from all of the included studies. The sheet was designed to extract the articles IDs, last author name, title, sample size, study design, the country where the study was conducted, and the assessed outcomes including the prevalence of overlap between IBS and GERD and the associated factors.

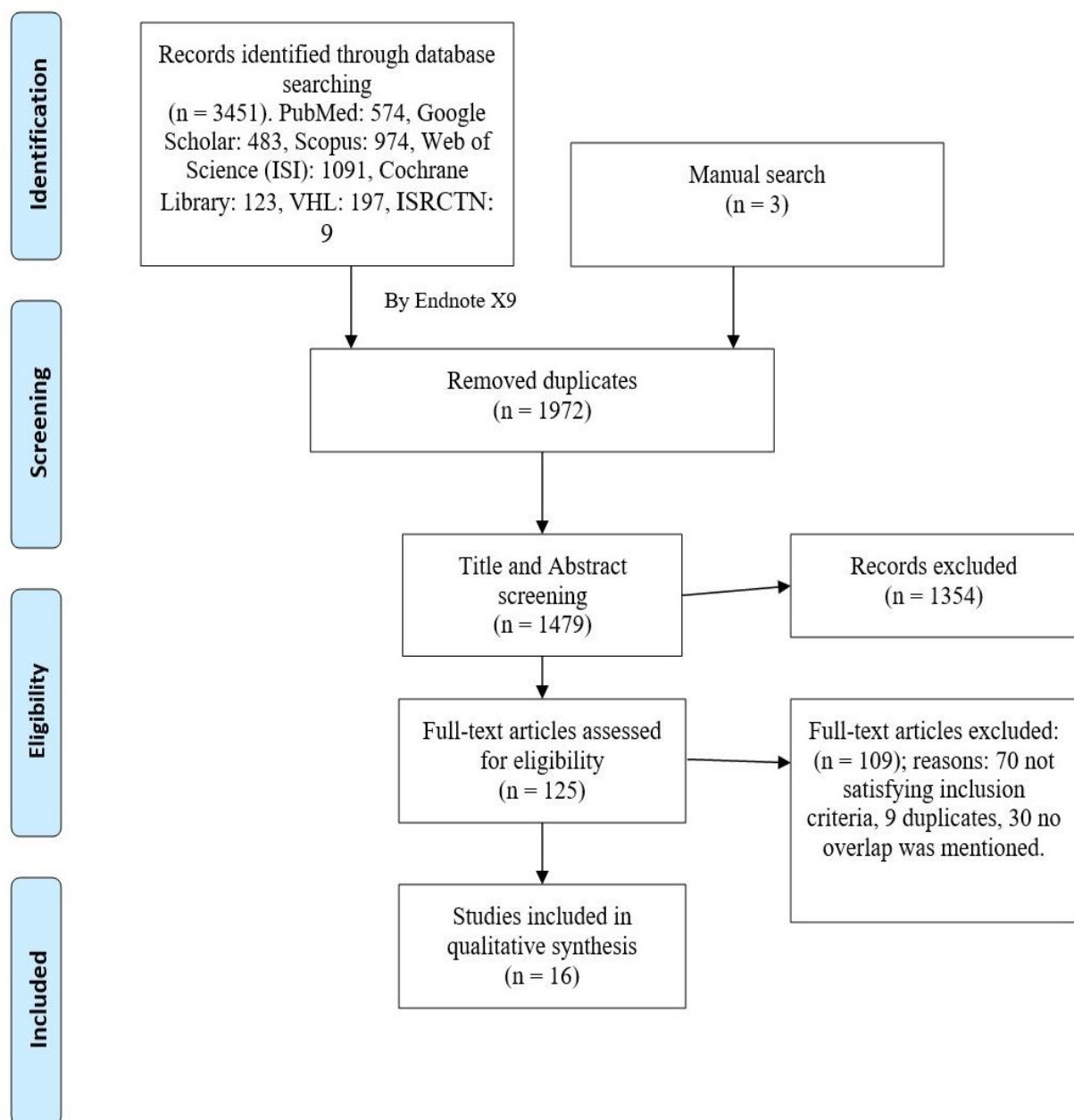
### Assessment of bias

For cross-sectional studies, the adjusted Newcastle-Ottawa scale NOS for cross-sectional studies was used, by which all studies were graded out of 10 according to the estimated quality (Newcastle-Ottawa 2011).<sup>13</sup> The tool was divided into three main categories including (1) the methodological quality of studies using five grades, (2) comparability of each study using two grades, (3) and the outcomes and statistical analysis using three grades. On the other hand, for randomized studies, the Cochrane Collaboration's proposal for the assessment of the risk of bias, by which, the following domains were assessed: selection, detection, performance, reporting, and attrition to classify studies as having low, some concerns, or high

risk of bias. This step was done by two reviewers and disagreements were resolved by discussion.<sup>14</sup>

### Search results

The total number of citations that were obtained by the thorough search strategy have reached 3,451. Using endnote, we excluded 1,972 duplicate articles and the remaining ones were prepared for the title and abstract screening. Among these articles, only 125 articles were eligible for full-text screening which resulted in the inclusion of 13 articles that met our inclusion criteria. We also managed to add another three articles to the overall list by manual search. The details of the search strategy and reasons for the excluded articles are presented in our flow diagram in Figure 1.



**Figure 1: PRISMA flow chart for the identification and selection processes of the included studies.**

Table 1: Risk of bias for the included cross-sectional studies by the adjusted Newcastle-Ottawa scale.

Author	Year	Selection				Comparability The subjects in different outcome groups are comparable	Outcome		Total score	Quality
		Representativeness of the Sample	Sample size	Non-respondents	Ascertainment of the exposure		Assessment of outcome	Statistical analysis		
Al Saadi et al	2019	+	+	+		+	+	+	6	Satisfactory
Baran et al	2017	+	+	+	+	+	+	+	7	Good
El Salhy et al	2019	+	+	+	+	+	+	+	7	Good
Ford et al	2013	+	+	+	+	++	+	+	8	Good
Fujiwara et al	2011	+	+			++	+	+	6	Satisfactory
Funaki et al	2017	+	+	+		++	+	+	7	Good
Lei et al	2019	+	+	+	+	+	+	+	7	Good
Martinucci et al	2011	+			+	+	+	+	5	Satisfactory
Morozova et al	2020	+	+	+	+	++	+	+	8	Good
Nam et al	2013	+	+	+	+	++	+	+	8	Good
Pourhoseingholi et al (1)	2012	+	+	+	+	+	+	+	7	Good
Pourhoseingholi et al (2)	2012	+	+			+	+	+	5	Satisfactory
Rasmussen et al	2015	+	+	+		++	+	+	7	Good
Wu et al	2011	+	+	+	++	+	+	+	8	Good

Table 2: Summary of the baseline characteristics of the included studies and the IBS/GERD overlap rates.

Reference	Year	Country	Study design	Sample size (n)	IBS or GERD (n)	Male (n)	Mean age (SD)	Investigations	IBS criteria	IBS/GERD (%)
Al Saadi et al <sup>29</sup>	2019	Syria	Cross-sectional	302	NS	106	21.6 (1.9)	Q	Rome III	4.6
Baran et al <sup>20</sup>	2017	Turkey	Cross-sectional	55	IBS	16	12.3 (3.8)	24-h pH	Rome III	41.80
El Salhy et al <sup>24</sup>	2019	Norway	Cross-sectional	1489	IBS	158	51	Q+ Endo+ blood tests	Rome III	66.00
Ford et al <sup>21</sup>	2013	United Kingdom	Cross-sectional	4003	GERD	1756	55.4 (2.8)	Q+H. pylori	Manning	15.8
Fujiwara et al <sup>26</sup>	2011	Japan	Cross-sectional	2680	NS	-	-	Q	Rome III	2.3
Funaki et al <sup>18</sup>	2017	Japan	Cross-sectional	37	IBS	12	60.7 (15.7)	Q + End	Rome III	64.9
Lei et al <sup>22</sup>	2019	Taiwan	Cross-sectional	273	GERD	136	50.4	Q	Rome III	9.50
Martinucci et al <sup>19</sup>	2011	Italy	Cross-sectional	46	IBS	15	51.1 (13.4)	Endoscopy+Q+24-h pH	Rome III	41.3
Mönnikes et al <sup>27</sup>	2012	Germany	RCT	634	NS	337	49.8 (14.3)	Q+ Endo+ <i>H. pylori</i>	Rome III	13.3
Mönnikes et al <sup>30</sup>	2011	Germany	RCT	1888	NS	910	47 (14.3)	Q + End	Q	15.00
Morozova et al <sup>25</sup>	2020	Russia	Cross-sectional	102	IBS	47	40.8	Endo+biopsy+x-ray+24-h pH	Rome III	20.6
Nam et al <sup>28</sup>	2013	Korea	Cross-sectional	2,769	NS	1682	-	Q + End	Rome III	1.70
Pourhoseingholi et al <sup>16</sup>	2012		Cross-sectional	18180	NS	7108	38.7 (17.1)	Q	ReQuest	34.00
Pourhoseingholi et al <sup>17</sup>	2012	Iran	Cross-sectional	18,180	IBS	9,090	38.7 (17.1)	Q	Rome III	74.70
Rasmussen et al <sup>15</sup>	2015	Denmark	Cross-sectional	95253	NS	5548	52 (40-66)	Q	Rome III	1.7
Wu et al <sup>23</sup>	2011	Hong Kong	Cross-sectional	265	GERD	98	46.2 (17.3)	Q+Endo+pH	Rome II	39.9

Q; symptom questionnaire; Endo; Endoscopy; RCT: Randomized controlled trial; NS; Non-specified; IBS: Irritable bowel syndrome; GERD: Gastroesophageal reflux disease; UK: United Kingdom.

## Risk of bias

The risk of bias assessment showed that ten of our studies had good results having a total score of 7-8 while the other studies had satisfactory results (total=5-6) with none of the studies having non-satisfactory results (total= 0-4). The detailed assessment and scores of all cross-sectional studies are presented in Table 1. Assessment of bias for two randomized controlled trials (RCTs) showed that both of them also had a low risk of bias totally and within all domains, except for reporting of the intended outcomes which had some concerns.

## Included studies characteristics

The total sample size that investigated the overlap between IBS and GERD in this study was 146,156 patients. The largest sample size was recorded by the registry-based study by Rasmussen et al (n=95,253) and the two cross-sectional studies conducted by Pourhoseingholi et al (n=18,180, each).<sup>15-17</sup> On the other hand, the smallest size was recorded by Funaki et al (n=37), Martinucci et al (n=46), and Baran et al (n=55).<sup>18,20</sup> At baseline, three studies included patients with GERD, six included patients with IBS, while seven included patients with non-specified GERD or IBS to study the correlation as to their primary outcome.<sup>15-18,21-30</sup> Almost all studies were cross-sectional in design while only two studies were RCTs.<sup>27,30</sup> All of the studies were published between 2011 and 2020 as presented in Table 2, together with other baseline characteristics and outcomes.

## DISCUSSION

### IBS and GERD diagnostic approaches

All of the included studies have reported the simultaneous occurrence of IBS and GERD patients. Almost all of the included studies assessed the presence of either of these disorders based on the clinical pictures that were obtained from their included patients by prepared questionnaires. Moreover, endoscopy, including the various types like esophagogastroduodenoscopy and colonoscopy, was also used to assess the status of the esophagus and stomach, in addition to the status of the bowel, for confirmation of GERD and IBS related lesions. Only three of the included studies used the 24-h pH monitoring for the assessment of gastric juice activity.<sup>19,20,25</sup> This test was previously considered the most sensitive laboratory test in diagnosing GERD and related gastro-esophageal lesions. Blood tests and *H. pylori* infection were also assessed by some studies for further confirmation of the diagnosis.<sup>21,27,30</sup> On the other hand, assessment and identification of IBS patients were based on Rome III criteria, while only one study depended on questionnaire-based diagnosis, one used the ReQuest questionnaire, one used the Manning approach, while only one study depended on the Rome II criteria.<sup>16,21</sup> The variability between the included studies in terms of the methods of diagnosis is probably due to the nature of data collection

in some studies which depended on retrospective data, however, almost all recent studies use the Rome III criteria almost exclusively. The effect of the applied diagnostic approach on the estimated overlap rates was clearly shown in a meta-analysis by Lovell et al who reported that the degree overlap was reduced to 14.2% when the Rome II criteria were used, from 26.7% when the Manning criteria were used for IBS patients.<sup>31</sup>

### Evidence of IBS and GERD overlap

Among the studies that reported the presence of GERD among IBS patients, pourhoseingholi et al reported the highest prevalence rate, being 74.7% GERD patients among 18,180 patients with IBS.<sup>16</sup> On the other hand, the lowest prevalence rate of patients with GERD among an IBS population was found to be 20.6%, however, the sample size was limited being 102 only as reported by Morozova et al.<sup>25</sup> Another four studies have also reported the prevalence of GERD symptoms among patients with IBS. A large study by El Slahy et al reported that 66% of their 1489 IBS patients were diagnosed with GERD.<sup>24</sup> A similar rate of 64.9% was also reported by Funaki et al, however, the sample size was too small which may have magnified the results.<sup>18</sup> The other two studies by Baran et al and Martinucci et al also reported similar rates, but lower than the previous two studies, as being 41.8%, and 41.3% for the two studies, respectively.<sup>19,20</sup>

On the other hand, the reported overlap rates were lower when IBS was investigated either in GERD or a non-specified population. Wu et al conducted a cross-sectional study to investigate the effect of the overlap of IBS and non-erosive reflux disease (NERD) when associated with inflammatory bowel diseases on the quality of life of the affected patients.<sup>23</sup> The reported overlap between NERD and IBS was 39.9%. In another study that was conducted by Ford et al, the authors reported that IBS occurred in 15.8% of their 4003 GERD population.<sup>21</sup> On the other hand, Lei et al reported a prevalence rate of 9.5% only.<sup>22</sup> In the studies which investigated the overlap between IBS and GERD with no baseline identification of neither of the disorders, the overlap prevalence rate ranged between 1.7% and 34%. It is worth mentioning that two of these studies were RCTs, and although investigating the overlap was not mainly among the study outcomes, we managed to obtain overlap results from the two studies' data being 15% and 13.3% in the two studies.<sup>27,30</sup> We have also noticed the lowest prevalence rate among the non-specified sample size studies was in the study where the largest sample size was estimated in our review.<sup>15</sup> So, this might raise questions about the potential effect of sample size on the reported outcomes, however, this was out of our review scope. We also noticed that studies with IBS baseline populations recorded the highest prevalence overlap rates which might also raise questions about whether IBS has a role in developing GERD more than GERD does on IBS, however, this also was not within the scope of this review and further studies are needed.<sup>16,18-20,24,25</sup>



### **Risk factors and pathophysiology for IBS and GERD overlap**

Although the diagnosis of this condition is mainly based on the clinical pictures of the affected patients, endoscopy and hematological examinations can aid in diagnosis indication, in addition to excluding the differential diagnoses.<sup>19,32</sup> Nam et al reported that somatization and anxiety were as significant risk factors for IBS as to NERD.<sup>28</sup> These factors, in addition to age, *H. pylori* infection, and smoking, significantly contributed to the development of GERD-related symptoms when they were in IBS patients. Fujiwara et al reported that female gender and cigarette smoking was associated with IBS and GERD overlap in their cross-sectional study.<sup>26</sup> In the study by Martinucci et al the authors noticed that IBS overlaps more frequently with functional heartburn than erosive and non-erosive reflux diseases.<sup>19</sup> In another study by Garros et al, who studied the overlap between IBS and patients receiving PPI for GERD, the authors reported a positive correlation between IBS and not responding to PPI treatment as the overlap rate was higher among these patients.<sup>33</sup> Baran et al also reported that treating functional constipation was associated with resolve in reflux symptoms in children that suffered from GERD and functional constipation overlap.<sup>20</sup> The meta-analysis by Lovell et al has also supported this as they showed that GERD symptoms were more likely to occur fourfold in IBS patients than other non-IBS patients.<sup>31</sup> These results might partially explain the possible association between IBS and GERD which might be attributable to the abnormal generalized motility of the digestive system and the harmful effect of gastric acid.<sup>34,35</sup> This is supported by the previous studies which reported a state of visceral hypersensitivity to a large number of stimuli as chemical, anatomical, and physical stimuli in both GERD and IBS.<sup>36,37</sup> Costantini et al has indicated this by showing that GERD symptoms increased in IBS patients when esophageal provocative tests were introduced, as compared to the control group.<sup>38</sup> Our reported results about the degree of GERD and IBS overlap are also consistent with the results by the previous reviews in 2013, and 2006.<sup>39,40</sup> The latter review has even demonstrated that IBS alone is not common and GERD increases the prevalence of the condition.

Our results might be limited to the small sample size in some of the included studies and the poor evidence that supports the pathophysiology of IBS and GERD overlap and the effect of either of them over the other, despite the significant association that was found in the literature.

### **CONCLUSION**

In this systematic review, we have found a strong correlation between IBS and GERD as indicated by the high prevalence rates of overlap by many of the included studies. However, the certain pathophysiology and risk factors behind this phenomenon remain non-clear and further studies are needed. The possible association

indicates the need for a proper management plan for these patients for better care and quality of life.

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